

## Cyclooxygenase-2 inhibitors: Will they help us prevent diabetic nephropathy?

In the past decades, end-stage renal disease (ESRD), with the consequent demand for renal replacement therapy (RRT), has evolved into a worldwide medical, social, and financial dilemma, which will likely be aggravated in coming years. Diabetic nephropathy accounts for a large fraction of the new cases of ESRD, an unfortunate circumstance considering the high frequency of cardiovascular complications, the early need for RRT, and the high dialysis-related morbidity that afflicts diabetic nephropathy patients.

In view of the magnitude of the current ESRD epidemics, no effort should be spared in the struggle to arrest or at least slow the progression of diabetic and other progressive nephropathies, thus postponing the need for RRT. Available treatments include immunosuppressors (mostly, but not exclusively, for immune-related nephropathies), dietary protein restriction, and, especially, angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers. Although these treatments have undoubtedly alleviated the social and financial burden imposed by progressive diabetic and nondiabetic nephropathies, a substantial fraction of treated patients still progress to ESRD. Clearly, the development of new renoprotective maneuvers is still badly needed.

Progressive nephropathies can be initiated by immune dysfunction, glomerular hemodynamic stress, and toxic aggression, among other mechanisms. In diabetic subjects, nonenzymatic protein glycation is also likely to play an important role in the pathogenesis of renal injury. There is mounting evidence that, whatever the mechanisms that initiate progressive nephropathies, an inflammatory reaction, involving the recruitment of macrophages, lymphocytes, fibroblasts and myofibroblasts, is required to extend and propagate the initial insult. Inflammatory cells can be found in the renal tissue prior to the establishment of glomerular and interstitial injury in several models of chronic nephropathy, including diabetic nephropathy [1]. Moreover, macrophage depletion prevents puromycin-induced renal injury, and treatment with the anti-lymphocyte agent, mycophenolate mofetil, attenuates renal injury in the renal ablation model [1].

Cyclooxygenase (COX) products are well-known me-

diators of inflammatory injury in arthritis and other conditions, and COX inhibition by nonsteroidal anti-inflammatory drugs (NSAIDs) has been largely employed in the treatment of arthritic patients. There is abundant evidence that COX products mediate inflammation in the kidneys as well. The synthesis of COX products by cultivated mesangial cells is enhanced by stretching [2], suggesting that they may mediate hemodynamically induced renal injury. In addition, COX products may participate in several immune and nonimmune cellular mechanisms of renal injury [3]. Up-regulation of both the COX-1 and COX-2 isoforms has been described in experimental glomerulopathies, while the production of COX derivatives is increased in the 5/6 renal ablation model [3]. Accordingly, NSAID treatment attenuated renal injury in the 5/6 renal ablation model without lowering glomerular pressure, suggesting a purely anti-inflammatory effect [4].

Several observations reported by Harris et al in the past 5 years have contributed to elucidate the role of COX-2 in progressive nephropathies. First, these investigators showed that COX-2 is expressed in the normal rat kidney, particularly at the macula densa region [5]. They next demonstrated that the expression of COX-2 was up-regulated in the 5/6 renal ablation model and that part of the extra COX-2 material located in the glomeruli [6]. In rats with aortic coarctation between the renal arteries, the group showed that COX-2 expression was augmented in the ischemic kidney and that administration of a selective COX-2 inhibitor, SC58236, attenuated the systemic hypertension and the hyper-reninemia associated with this model [7]. In rats with 5/6 renal ablation, administration of the same compound attenuated proteinuria and prevented glomerulosclerosis as efficiently as enalapril [8], lending further support to the idea that COX-2 activation plays an important role in the pathogenesis of progressive renal injury.

In continuation of this line of investigation, Cheng et al, in a study published in the current issue of *Kidney International* [9], examined a model of experimental diabetes associated with hypertension, in which streptozotocin diabetes was combined with deoxycorticosterone (DOCA)-salt treatment. In this model, which mimics the quite common clinical association of diabetes and hypertension, glomerular injury progressed at a faster rate than in rats with diabetes or DOCA-salt alone, re-

sulting in severe proteinuria and significant glomerulosclerosis after 6 weeks. The renal expression of COX-2 was increased, along with that of fibronectin, transforming growth factor-beta (TGF- $\beta$ ) and plasminogen-activator inhibitor (PAI-1), suggesting involvement of these mediators in the pathogenesis of renal injury in this model. Cheng et al showed that the administration of SC58236 to these rats reduced the expression of all the mediators examined and prevented the development of glomerulosclerosis, lending support to the idea that elements of chronic inflammation and COX-2-derived prostanoids play a key pathogenic role in diabetic nephropathy. The potential practical implications of these findings are evident, since COX-2 inhibitors are easily available drugs, which are, in general, much better tolerated than nonspecific COX inhibitors and can be as easily used as ACE inhibitors in routine therapeutic schemes.

Despite the positive results reported by Cheng et al [9] and by others [4, 8], much remains to be learned before we can accept COX-2 inhibitors as routine renoprotective agents. First, the present results will obviously have to be confirmed in other experimental studies and, especially, in controlled clinical trials. Second, the chronic use of COX-2 inhibitors requires special caution, since these compounds, much in the same manner as conventional NSAIDs, are far from innocuous. COX-2 inhibitors have been reported to promote sodium retention, leading to edema formation and elevated blood pressure [10]. More important, several cases of acute renal failure presumably caused by the use of COX-2 inhibitors, particularly in individuals with sodium depletion and hypovolemia, have been anecdotally reported, although the overall risk of such accidents appears to be modest. It must be stressed that other drugs with potentially dangerous untoward effects, such as cyclosporine (renal fibrosis) and ACE inhibitors (hyperkalemia, acute renal

failure), have been widely and successfully employed in the management of progressive nephropathies. If the efficacy of COX-2 inhibitors as renoprotective agents is proven, their clinical use will also have to be governed by careful individual risk/benefit evaluation.

ROBERTO ZATZ and CLARICE KAZUE FUJIHARA  
São Paulo, Brazil

Correspondence to Roberto Zatz, M.D., Ph.D. Laboratório de Fisiopatologia Renal Avenida Doutor Arnaldo, 455, 3-s/3342 01246-903 São Paulo SP Brazil.  
E-mail: rzatz@usp.br

## REFERENCES

1. RODRIGUEZ-ITURBE B, PONS H, HERRERA-ACOSTA J, JOHNSON RJ: Role of immunocompetent cells in nonimmune renal diseases. *Kidney Int* 59:1626–1640, 2001
2. AKAI Y, HOMMA T, BURNS KD, *et al*: Mechanical stretch/relaxation of cultured rat mesangial cells induces protooncogenes and cyclooxygenase. *Am J Physiol* 267:C482–C490, 1994
3. HARRIS RC: Cyclooxygenase-2 in the kidney. *J Am Soc Nephrol* 11:2387–2394, 2000
4. FUJIHARA CK, MALHEIROS DM, DONATO JL, *et al*: Nitroflurbiprofen, a new nonsteroidal anti-inflammatory, ameliorates structural injury in the remnant kidney. *Am J Physiol* 274:F573–F579, 1998
5. HARRIS RC, MCKANNA JA, AKAI Y, *et al*: Cyclooxygenase-2 is associated with the macula densa of rat kidney and increases with salt restriction. *J Clin Invest* 94:2504–2510, 1994
6. WANG JL, CHENG HF, ZHANG MZ, *et al*: Selective increase of cyclooxygenase-2 expression in a model of renal ablation. *Am J Physiol* 275:F613–F622, 1998
7. WANG JL, CHENG HF, HARRIS RC: Cyclooxygenase-2 inhibition decreases renin content and lowers blood pressure in a model of renovascular hypertension. *Hypertens* 34:96–101, 1999
8. WANG JL, CHENG HF, SHAPPELL S, HARRIS RC: A selective cyclooxygenase-2 inhibitor decreases proteinuria and retards progressive renal injury in rats. *Kidney Int* 57:2334–2342, 2000
9. CHENG HF, WANG CJ, MOECKEL GW, *et al*: Cyclooxygenase-2 inhibitor blocks expression of mediators of renal injury in a model of diabetes and hypertension. *Kidney Int* 62:929–939, 2002
10. ZHAO SZ, REYNOLDS MW, LEJKOWITH J, *et al*: A comparison of renal-related adverse drug reactions between rofecoxib and celecoxib, based on the World Health Organization/Uppsala Monitoring Centre safety database. *Clin Ther* 23:1478–1491, 2001